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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/806,088
Filing Date: March 22, 2004
Appellant(s): FLACK ET AL.

John Kilyk, Jr.
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed August 17, 2007 appealing from the Office Action mailed March 19, 2007.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Wu *et al.* (Cancer Research, 1989, vol. 49, pages 3754-3758)

Band *et al.* (Gynecologic Oncologists, 1986, vol. 23, page 261)

Zhang *et al.* (Acta Academiae Medicinae Sinicae, 1985, vol. 7, pages 384-387)

Wu *et al.* (Clin. Pharmacol. Ther., 1986, vol. 39, pages 613-618)

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 8-10, 16 and 38-43 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Wu *et al.* (Cancer Research, 1989, vol. 49, pages 3754-3758) (prior art of record) in view of Band *et al.* (Gynecologic Oncologists, 1986, vol. 23, page 261) (prior art of record) and Zhang *et al.* (Acta Academiae Medicinae Sinicae, 1985, vol. 7, pages 384-387) (cited by applicants in IDS filed 5/1/2006).

The instant claims are drawn to the treatment of cancer in humans comprising the administration of (-)-gossypol.

Wu *et al.* disclose the *in vitro* and *in vivo* antitumor activity of gossypol in human SW-13 adrenocortical carcinoma cells (Abstract). It is disclosed that gossypol was known in the art to exhibit a broad spectrum of activities, including antitumor activity. For example, gossypol was known to lengthen the survival of 10-12 week old mice bearing mouse mammary adenocarcinoma and was effective against cells originating from a rat testicular tumor (page 3754). The authors demonstrate that gossypol inhibits the proliferation of SW-13 adrenocortical carcinoma cells *in vitro* (Figure 2). Further, gossypol caused a decrease in the cumulative tumor

surface area of SW-13 tumors in mice (Figure 7). Only two deaths were observed in the gossypol-treated mice, compared to ten deaths in the control group (page 3756, left column). Tumor prevalence and tumor size were both decreased in the gossypol-treated group of mice (Tables 2 and 3). The authors conclude, "These data suggest that gossypol may provide a beneficial effect in patients with adrenocortical carcinoma by decreasing the overall tumor burden and prolonging their duration of survival" (page 3758). The reference thus provides one skilled in the art with the motivation to administer gossypol to humans to treat cancer.

Band *et al.* disclose that low oral doses of gossypol is used as an effective male oral contraceptive with the only detectable side effect being hypokalemia. The reference thus demonstrates that gossypol can be safely administered to humans. The authors studied the cytotoxic effect of gossypol on reproductive cancer cell lines of ovarian, testicular and gestational origin. Cancer cell lines were significantly more sensitive to gossypol than normal human cells of high mitotic activity, fibroblast cell lines, and PHA-stimulated lymphocytes. The tumor growth inhibitory activity of gossypol is "primarily attributable to the (-)-isomer which is 3.6 –9.3 times more potent than the (+)-isomer". The reference thus provides the skilled artisan with the motivation to administer (-)-gossypol as opposed to racemic gossypol. The authors conclude (emphasis added):

> "Considering the established absence of side effects in the administration of low doses of gossypol to humans, these data suggest that (-)-gossypol, alone or in combination with other drugs, may be useful clinically in the treatment of cancer of reproductive tract origin."

The reference thus provides further motivation to administer gossypol to humans to treat cancer.

Zhang *et al.* is provided as evidence that (-)-gossypol was effective in another preclinical model of anticancer activity. The reference discloses that (-)-gossypol inhibited the cell growth,

DNA synthesis, and cell division of HeLa cell cultures, whereas (+)-gossypol had no effect. The effective concentration of (-)-gossypol was 2-fold less than that of racemic gossypol, suggesting that the antitumor activity of racemic gossypol is due to the (-)-isomer (Abstract). The reference thus provides one skilled in the art further motivation to administer (-)-gossypol to treat cancer.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to administer (-)-gossypol to human patients in order to treat cancer because preclinical models of cancer treatment clearly suggest that such treatment would be effective. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

In the instant case, the prior art establishes that gossypol: 1) can be safely administered to humans in low oral doses; 2) is an effective antitumor agent *in vivo* and *in vitro*; and 3) is more effective as the (-)-isomer than the (+)-isomer. The prior art does not explicitly disclose the administration of gossypol to humans to treat cancer. However, one skilled in the art would recognize that the models of antitumor activity disclosed in the references are often used to discover new chemotherapeutic agents. As such, the skilled artisan would have been imbued with at least a reasonable expectation that administration of (-)-gossypol to a human having cancer would be effective in treating said cancer. While antiproliferative and antitumor activity *in vitro* and *in vivo* models does not always correlate with activity in humans, the skilled artisan

would have been imbued with a reasonable expectation that (-)-gossypol would be effective in treating human cancers.

It is apparent from the prior art that administration of gossypol to humans was known to be safe (Band *et al.*). Thus, the administration to humans instantly claimed would have been *prima facie* obvious and the skilled artisan would reasonably expect that no serious side effects would occur upon such administration. It is also apparent from the prior art that gossypol was known to be an effective antitumor agent in preclinical models of cancer (Wu *et al.* and Zhang *et al.*). Thus, the treatment of cancer with gossypol would have been *prima facie* obvious and the skilled artisan would reasonably expect that administration of gossypol to a human having cancer would effectively treat the cancer. With respect to the administration of (-)-gossypol, it is clear from the prior art that one skilled in the art would have reasonably expected that (-)-gossypol is more effective than (+)-gossypol (Band *et al.* and Zhang *et al.*). As such, it would have been *prima facie* obvious to administer (-)-gossypol to treat cancer in a human patient. This is especially true given that (-)-gossypol was known to be effective in inhibiting the cell growth, DNA synthesis, and cell division of HeLa cell cultures as disclosed in Zhang *et al.* as well as being effective *in vivo* as disclosed in Wu *et al.*

Thus, the skilled artisan would have had the motivation to administer (-)-gossypol to humans to treat cancer as well as a reasonable expectation of success in treating said cancer.

Claims 11-14 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Wu *et al.*, Band *et al.* and Zhang *et al.* as applied to claims 8-10, 16 and 38-43 above and further in view of Wu *et al.* (Clin. Pharmacol. Ther., 1986, vol. 39, pages 613-618) (prior art of record).

Instant claims 11-14 recite a specific blood concentration of (-)-gossypol as well as doses and administration routes of (-)-gossypol.

Wu *et al.* (1989), Band *et al.* and Zhang *et al.* disclose as discussed *supra.* Wu *et al.* (1986) disclose pharmacokinetic studies of racemic, (+)- and (-)-gossypol in humans and dogs (Abstract). (-)-Gossypol was administered to humans at a dose of 20 mg (page 614, left column). Mean plasma levels of (-)-gossypol are shown in Figure 2. These levels fall within the instantly claimed range. In view of the Wu *et al.* disclosure, it would have been *prima facie* obvious to modify the administration routes and doses of (-)-gossypol to affect the optimal combination of pharmacokinetics and efficacy in the treatment of cancer in humans. Such optimization of dosing schedule, administration routes and doses is routine in the art of chemotherapy.

(10) Response to Argument

With respect to claims 8-10, 16, and 38-43, Appellants appear to predicate patentability of their claimed methods of treating cancer in human patients *via* administration of (-)-gossypol on the fact that the prior art does not *explicitly* teach that (-)-gossypol is effective to treat cancer in humans. However, if such were the case, the Examiner would have made rejections under 35 U.S.C. § 102, not 35 U.S.C. § 103 as is the case here. In the instant case, it is the Examiner's position that a preponderance of the evidence suggests that the instantly claimed methods would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Appellants submit that the Examiner has erred in determining the scope and content of the prior art by not considering prior art, which Appellants assert taught away from the practice

of the invention. In support of this argument, Appellants cite Band (Gynecologic Oncology, 1989, vol. 32, pages 272-277) wherein the data at Table 1 on page 276 shows that (-)-gossypol is non-selective with respect to cell type. However, the Examiner is unaware of any clinically used anticancer drug that is not toxic to normal, non-cancerous cells to some extent. As such, the fact that (-)-gossypol is non-selective (*i.e.*, inhibits the growth of both cancerous and non-cancerous cells) does not teach away from the use of this compound to treat cancer in humans. The Examiner's position is further supported by the fact that Band *et al.* (1986), as cited by the Examiner in the present rejections, discloses that low oral doses of gossypol are used as an effective male oral contraceptive with the only detectable side effect being hypokalemia. Further, Band *et al.* (1989) as cited by Appellants, also teaches at page 276, right column, that the "lack of any reported *in vivo* side effects attributable to such [general antiproliferative] activity is surprising." Further still, Wu *et al.* (1986) disclose pharmacokinetic studies of racemic, (+)- and (-)-gossypol in humans and dogs (Abstract). There are a plethora of other references that disclose administration of gossypol to human patients with limited toxicity. As such, it is the Examiner's position that the totality of the prior art suggests that (-)-gossypol can be safely administered to human patients.

A more important question, however, is not whether (-)-gossypol is safe, but whether the skilled artisan would have been imbued with **at least a reasonable expectation** that it would be an effective treatment for cancer in human patients. As discussed *supra*, the prior art teaches that (-)-gossypol has activity in preclinical models of cancer, both *in vitro* and *in vivo*. As *in vitro* and *in vivo* assays are well accepted in the art of anticancer research as effective models of human cancer and are used by nearly every pharmaceutical company in the world to screen for

potential new anticancer agents, the Examiner is at a loss to explain why Appellants do not consider the positive effects of (-)-gossypol in such models as motivation to try (-)-gossypol in the treatment of cancer in human patients. If the standard for establishing obviousness in cases relating to the treatment of diseases and disorders in human patients required the Examiner to prove that the claimed drug is safe and effective in human patients, the only prior art available to the Examiner would be the results of Phase II or Phase III clinical trials. However, just as Appellants are not required to have FDA approval in order to patent methods of treating human patients, neither does the Examiner have to prove the safety and efficacy in human patients in order to establish a *prima facie* case of obviousness. All that is required to establish a prima facie case of obviousness is a *reasonable expectation* of success. The fact that (-)-gossypol was shown to be effective in preclinical models of cancer clearly provides such a reasonable expectation of success in treating human patients.

Further, during prosecution Appellants submitted evidence that (-)-gossypol is safe and effective in treating cancer in human patients (see Holmlund Declaration filed October 20, 2006). Appellants assert that this showing "is surprising and further evidences the unobviousness of the claimed invention." However, it is the Examiner's position that this showing only demonstrates that which he set forth as *prima facie* obvious: that (-)-gossypol would be a safe and effective treatment for cancer in human patients.

Appellant's arguments with respect to claim 11-14 echo those made with respect to claims 8-10, 16, and 38-43. Accordingly, the Examiner refers to the discussion *supra* with the additional comment that determining optimal administration schedules, routes, and doses is routine in the art of drug administration and well within the purview of the skilled artisan.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Examiner James D. Anderson

Conferees:

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